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(58) Field of search

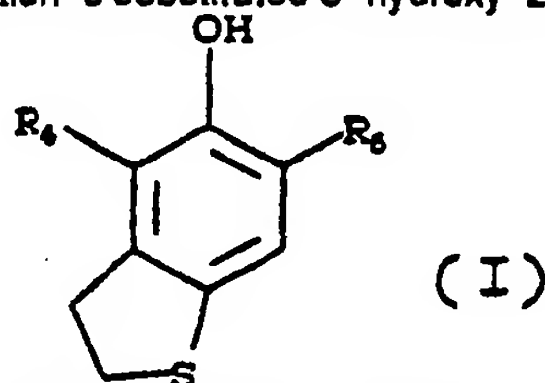
UK CL (Edition J) C2C CQT CWD

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Online databases: CAS ONLINE

(54) **Substituted 5-hydroxy-2,3-dihydrobenzothiophenes as inhibitors of leukotriene biosynthesis**

(57) Position-4 and/or position-6 substituted 5-hydroxy-2,3-dihydrobenzothiophenes of the following general structural formula (I) are disclosed:



These compounds and their salts are found to be potent inhibitors of leukotriene biosynthesis.
In the above formula, R₄ and R₅ are hydrogen, alkyl, alkenyl or phenylthioalkyl.

0020/CCP2

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TITLE OF THE INVENTION

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SUBSTITUTED 5-HYDROXY-2,3-DIHYDROBENZOTHIOPHENES AS
INHIBITORS OF LEUKOTRIENE BIOSYNTHESIS

BACKGROUND OF THE INVENTION

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The present invention relates to novel
fourth and/or sixth position substituted 5-hydroxy-
2,3-dihydrobenzothiophenes useful as inhibitors of
leukotriene biosynthesis.

Copending U.S. Patent Application Serial No.
230,825 (CN 17729) of Caldwell et al filed

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August, 12, 1988, corresponding to GB8917714.1, discloses fourth and/or sixth position substituted 5-hydroxy-2,3-dihydrobenzofurans useful as inhibitors of leukotriene biosynthesis.

5 During the progression of inflammatory conditions, there is generally an appearance and/or presence of macrophages and lymphocytes, especially polymorphonuclear leukocytes. These cells are known to secrete various products in response to
10 inflammatory stimuli. The arachidonic acid oxygenation products, in particular, have been identified as the critical mediators of various inflammatory conditions. Inhibition of arachidonic acid oxidation by enzyme inhibition has been explored
15 as effective therapy. For example, non-steroidal anti-inflammatory drugs (NSAID) such as aspirin, indomethacin and diflunisal are known cyclooxygenase inhibitors which inhibit the process wherein
20 arachidonic acid is oxygenated via cyclooxygenase to prostaglandins and thromboxanes.

 Recently, it has been observed that certain leukotrienes are responsible for diseases related to immediate hypersensitivity reactions such as human
25 asthma, allergic disorders, and skin diseases. In addition, certain leukotrienes and derivatives thereof are believed to play an important role in causing inflammation (B. Samuelsson, Science, 220, 568 (1983); D. Baily et al, Ann. Rpts. Med. Chem., 17, 203 (1982)).

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5 Accordingly, pharmacological agents which are
capable of inhibiting the formation or the release of
a mediator and thereby interfere with the function of
macrophages or polymorphonuclear leukocytes may also
be effective agents in the treatment of various
inflammatory conditions, e.g., pain, fever, rheumatoid
arthritis, osteoarthritis, bronchial inflammation,
10 inflammatory bowel disease, asthma, allergic
disorders, skin diseases, cardiovascular disorder,
glaucoma, emphysema, acute respiratory distress
syndrome, spondylitis, lupus, gout and psoriasis.

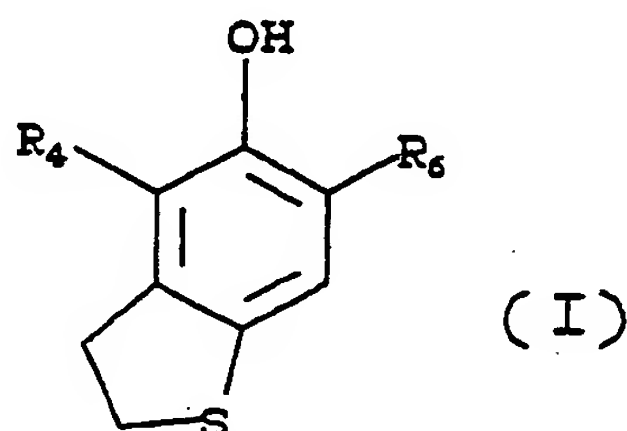
15 The human polymorphonuclear leukocytes
assay, has been found to be a useful indicator of the
ability of compounds to inhibit leukotriene
biosynthesis. Known inhibitors of leukotriene
biosynthesis, agents such as phenidone and
nordihydroguaiaretic acid, for example, are active in
this assay (C. J. Blackwell and R. J. Flower,
20 Prostaglandins, 16, 417 (1978); J. Chang, M.D.
Skowronek, M. L. Cherney and A. J. Lewis,
Inflammation, 8, 143 (1984)).

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DETAILED DESCRIPTION OF THE INVENTION

5 This invention relates to novel compounds of
formula (I)



wherein:

15 R₄ and R₆ are independently:

- (a) hydrogen;
- (b) C₂₋₆alkenyl;
- (c) C₃₋₆alkyl;
- (d) substituted C₃₋₆alkyl wherein the

20 substituent is phenylthio,
or pharmaceutically acceptable salts thereof.

In a preferred embodiment of the instant
invention, the compounds of formula (I),

25 R₄ is hydrogen; and

R₆ is (a) C₃₋₄alkenyl;
(b) C₃₋₄alkyl;
(c) phenylthio substituted C₃₋₄alkyl.

30

Specific species of the preferred embodiment are:

- 5
- (a) 6-(propen-3-yl)-5-hydroxy-2,3-dihydro-benzothiophene;
 - (b) 6-propyl-2,3-dihydro-5-hydroxybenzothiophene;
 - 10 (c) 6-t-butyl-2,3-dihydro-5-hydroxybenzothiophene; and
 - (d) 5-hydroxy-2,3-dihydro-6-(3-thiophenoxy-propyl)-benzothiophene,

15 or pharmaceutically acceptable salts thereof.

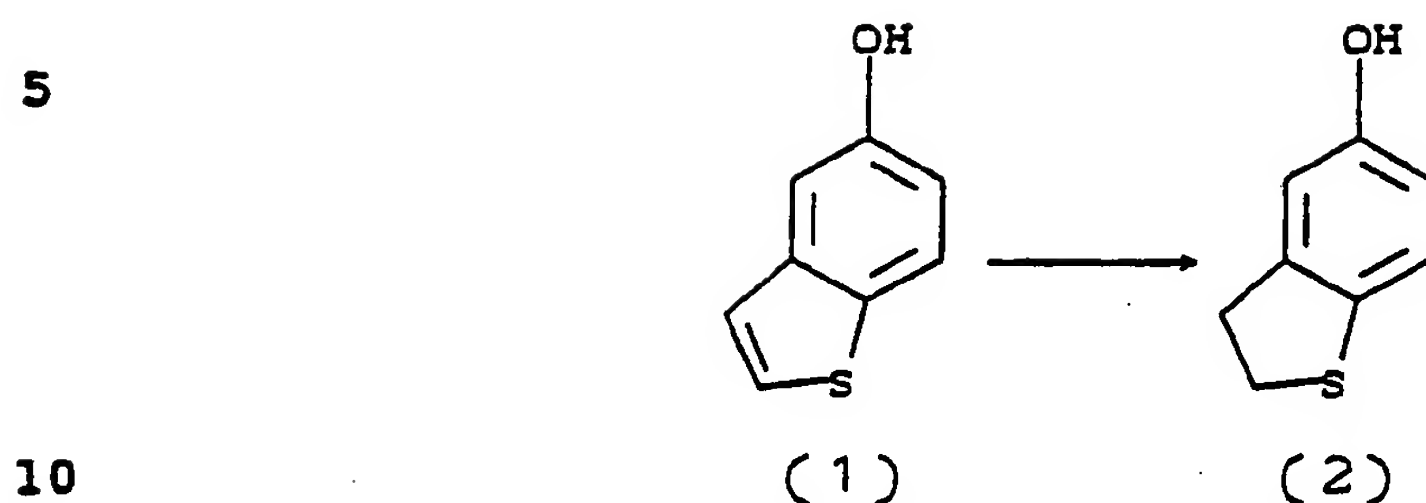
Less preferred species of the instant invention are:

- 20
- (a) 5-hydroxy-2,3-dihydrobenzothiophene; and
 - (b) 4-(propen-3-yl)-5-hydroxy-2,3-dihydro-benzothiophene.

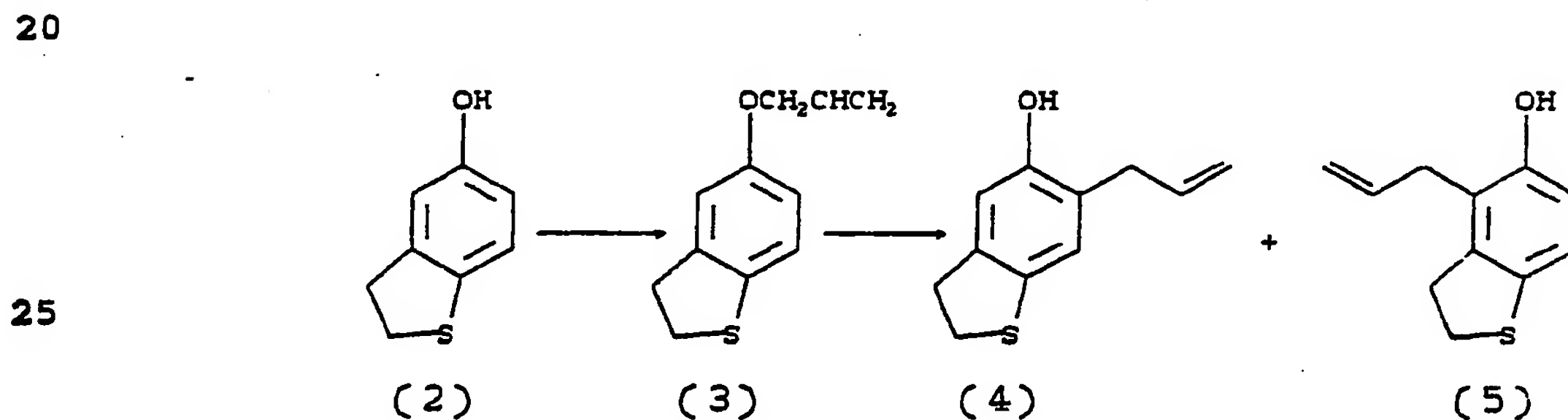
25 The compounds of the present invention are conveniently prepared using the procedures described generally below and more explicitly in the specific Examples thereafter.

The terms R_4 and R_6 are as defined in formula I and depict the point of substitution.

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SCHEME I

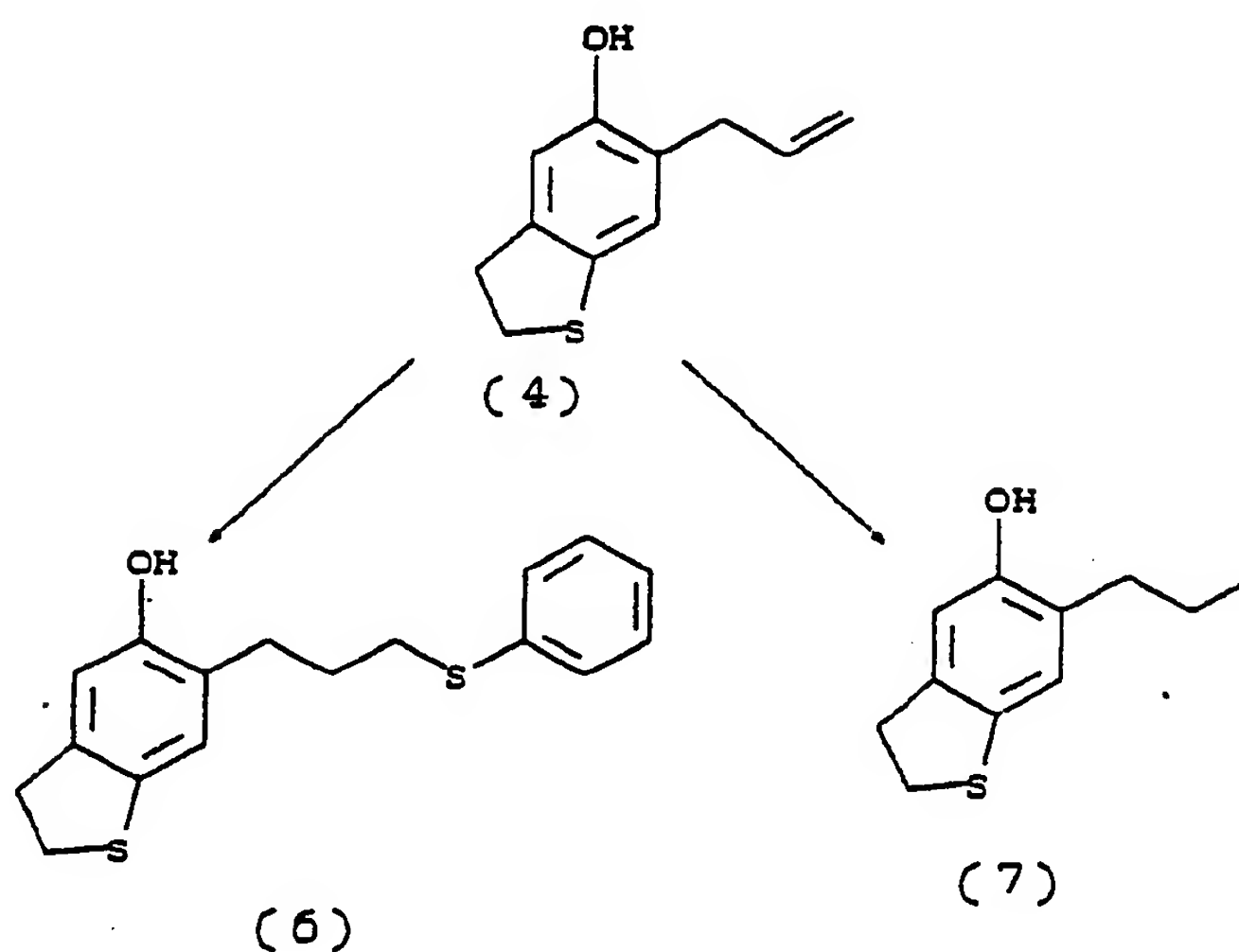
Scheme I depicts the preparation of the simplest member (2) of the invention, that is where R_4 and R_6 are both hydrogen. Triethylsilane is reacted with 5-hydroxybenzothiophene in a suitable solvent, e.g. trifluoroacetic acid (TFA) to yield the 5-hydroxy-2,3-dihydrobenzothiophene.

SCHEME II

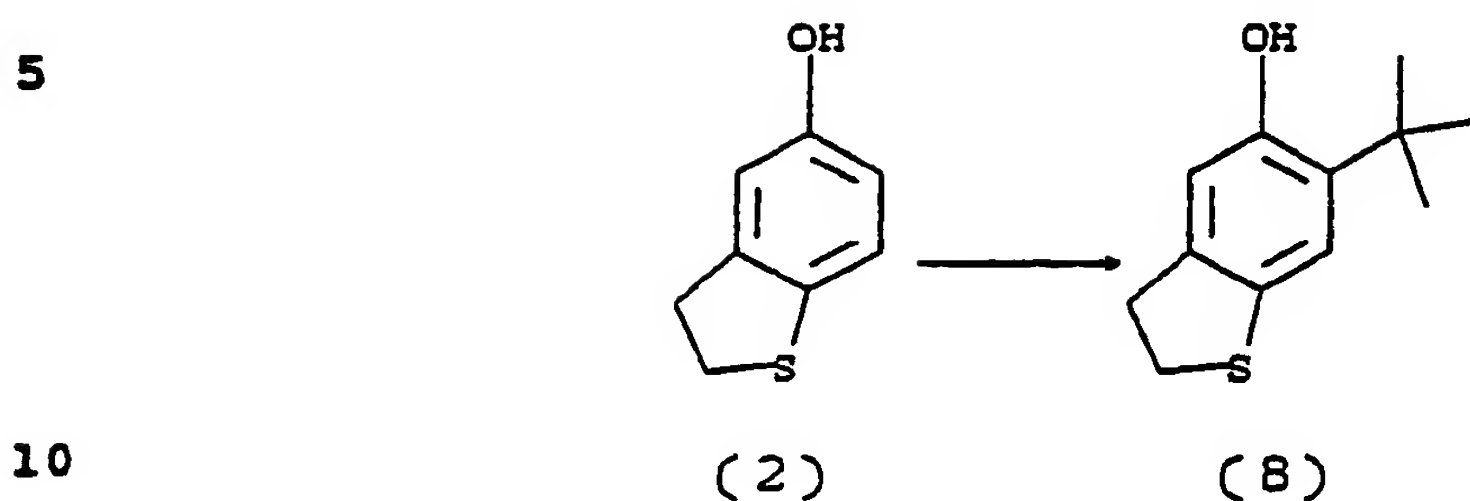
In reaction Scheme II, compound (2) is reacted with an alkenyl halide to form the corresponding 5-alkenyloxy-2,3-dihydrobenzothiophene (3). This in turn, by Claisen

rearrangement, yields a mixture of the corresponding 4-alkenyl and 6-alkenyl-5-hydroxy-2,3-dihydrobenzothiophenes.

SCHEME III



In reaction Scheme III, the 6-alkenyl-5-hydroxy-2,3-dihydrobenzothiophene is reacted with thiophenol in the presence of a free radical initiator, e.g. azobisisobutyronitrile (AIBN) to yield the corresponding phenylthio substituted alkyl (6). Alternatively, the alkenyl can be reduced to the unsubstituted alkyl (7). While Scheme III shows reaction with the 6-alkenyl-5-hydroxy-2,3-dihydrobenzothiophene, the corresponding 4-alkenyl 5-hydroxy-2,3-dihydrobenzothiophene reacts in the same manner to yield the corresponding 4-alkenyl homolog.

SCHEME IV

Alternatively, in reaction Scheme IV, the 5-hydroxybenzothiophene is reacted in suitable solvent with a tertiary alkanol using concentrated H₂SO₄ or another suitable acid catalyst to yield the 6-alkyl-5-hydroxy-2,3-dihydrobenzothiophene. While the t-butyl is shown, substitution of the appropriate tertiary alkanol could as easily have yielded other C₃₋₆ alkyls.

20 This invention also relates to a method of treating inflammation in patients in need of such treatment. Generally, an effective non-toxic amount of a compound of formula (I) or a pharmaceutical composition thereof, particularly an especially preferred compound, is administered to the patient as the active constituent.

25 To demonstrate the utility of the present invention, representative novel compounds of formula I were evaluated for their ability to inhibit production of leukotriene B₄ (LTB₄) in isolated rat and human polymorphonuclear leukocytes (PMN). Other compounds known to inhibit leukotriene biosynthesis have been shown to have activity in this assay, and thus the assay is of value in predicting in vivo activity. The assay is conducted as follows:

30

5 A. Preparation of Human PMN. Human blood is
obtained by antecubital venepuncture from consenting
volunteers who denied having taken medication within
the previous 7 days. The blood is immediately added
to 10% (v/v) trisodium citrate (0.13 M) or 5% (v/v)
sodium heparin (1000 IU/mL). PMNs are isolated from
anticoagulated blood by dextran sedimentation and
centrifugation through Ficoll-Hypaque (specific
gravity 1.077), essentially as described by Boyum.
10 (Boyum, A., Scand. J. Clin. Lab. Invest. 1968, 21
(Supp 97), 77). Contaminating erythrocytes are
removed by lysis following exposure to ammonium
chloride (0.16 M) in Tris buffer (pH 7.65), and the
PMNs resuspended at 5×10^5 cells/mL in HEPES (15 mM)
15 buffered Hanks balanced salt solution containing Ca^{2+}
(1.4 mM) and Mg^{2+} (0.7 mM), pH 7.4. Viability is
assessed by Trypan blue exclusion and is typically
greater than 98%.

20 B. Rat Peritoneal Polymorphonuclear
leukocytes (PMN). Male Sprague-Dawley rats were
purchased from Taconic Farms, Germantown, NY. The
animals were maintained on standard pellet diet and
water ad lib. Elicited PMN were prepared from
25 peritoneal exudates as follows: 8 ml of 12% sodium
caseinate was injected intraperitoneally into male
rats. After 18-20 hours, the rats were killed with
 CO_2 and the peritoneal cavities were lavaged with
Eagle's MEM (pH 7.7) without NaHCO_3 but containing
30 Earle's salts, L-glutamine, and 30 mM HEPES. The PMN
were isolated by centrifugation, washed with MEM,
filtered through lens paper to remove clumps, and
adjusted to a concentration of 1×10^7 cells/ml.

C. Generation and Radiomunoassay of LTB₄.

5 PMNs (0.5 mL; 2.5×10^5 cells) are placed in plastic tubes and incubated (37°C, 2 min) with test compounds at the desired concentration or vehicle control (DMSO, final concentration 0.2%). The synthesis of LTB₄ is initiated by the addition of calcium ionophore A23187 (final concentration 10 μ M) or vehicle on control samples and allowed to proceed for 5 minutes at 37°C. The reactions are then terminated by the addition of cold methanol (0.25 mL) and samples of the entire PMN reaction mixture are removed for radiomunoassay of LTB₄.

10 Samples (50 μ l) of authentic LTB₄ of known concentration in radiomunoassay buffer (RIA) buffer (potassium phosphate 1mM; disodium EDTA 0.1 mM; Thimerosal 0.025 mM; gelatin 0.1%, pH 7.3) or PMN reaction mixture diluted 1:1 with RIA buffer are added to reaction tubes.

15 Thereafter [³H]-LTB₄ (10 nCi in 100 μ l RIA buffer) and LTB₄ antiserum (100 μ L of a 1:3000 dilution in RIA buffer) are added and the tubes vortexed. Reactants are allowed to equilibrate by incubation overnight at 4°C. To separate antibody-bound from free LTB₄, aliquots (50 μ L) of activated charcoal (3% activated charcoal in RIA buffer containing 0.25% Dextran T-70) were added, the tubes vortexed, and allowed to stand at room temperature for 10 minutes prior to centrifugation (1500 x g; 10

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min; 4°C). The supernatants containing antibody-bound LTB₄ are decanted into vials and Aquasol 2 (4 mL) was added. Radioactivity is quantified by liquid scintillation spectrometry. Preliminary studies established that the amount of methanol carried into the radioimmunoassay did not influence the results. The specificity of the antiserum and the sensitivity of the procedure have been described in detail elsewhere. (Rokach, J.; Hayes, E. C.; Griend, Y.; Lombardo, D. L.; Maycock, A. L.; Rosenthal, A. S.; Young, R. N.; Zamboni, R.; Zweerink, H. J. Prostaglandins Leukotrienes and Medicine 1984, 13, 21). The amount of LTB₄ produced in test and control (approx. 20ng/10⁶ cells) samples are then calculated. Inhibitory dose-response curves are constructed using a four-parameter algorithm and from these the IC₅₀ values are determined.

Standard compounds phenidone and nordihydroguaiacetic acid, when evaluated by the above described in vitro test, demonstrate IC₅₀ values for LTB₄ inhibition of 9250 nM and 86 nM respectively. As also indicated below representative compounds within the scope of the present invention have been found to possess in vitro activities superior to those of these standard compounds.

Polymorphonuclear Leucocyte (PMN) Activity of Specific Compounds

5	R ₄	R ₆	Rat PMN	Human PMN
			<u>IC₅₀ (nM)</u>	<u>IC₅₀ (nM)</u>
	H	H	5230	
	H	-CH ₂ CH=CH ₂	190	319
	H	-C ₃ H ₈	211	326
10	H	-C ₄ H ₁₀	207	142
	-CH ₂ CH=CH ₂	H	887	2259

15 For the treatment of inflammation, arthritis conditions, psoriasis, asthma, or other diseases mediated by prostaglandins, a compound of formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic

20 pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intravascular injection or infusion techniques. In addition to the treatment of

25 warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

30 The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or

5 granules, emulsions, hard or soft capsules, or syrups
or elixirs. Compositions intended for oral use may be
prepared according to any method known to the art for
the manufacture of pharmaceutical compositions and
such compositions may contain one or more agents
selected from the group consisting of sweetening
agents, flavoring agents, coloring agents and pre-
serving agents in order to provide pharmaceutically
elegant and palatable preparations. Tablets contain
the active ingredient in admixture with non-toxic
pharmaceutically acceptable excipients which are
suitable for the manufacture of tablets. These
excipients may be for example, inert diluents, such
as calcium carbonate, sodium carbonate, lactose,
calcium phosphate or sodium phosphate; granulating
and disintegrating agents, for example, corn starch,
or alginic acid; binding agents, for example starch,
gelation or acacia, and lubricating agents, for
example magnesium stearate, stearic acid or talc.
The tablets may be uncoated or they may be coated by
known techniques to delay disintegration and
absorption in the gastrointestinal tract and thereby
provide a sustained action over a longer period. For
example, a time delay material such as glyceryl
monostearate or glyceryl distearate may be employed.
They may also be coated by the techniques described
in the U.S. Patent Nos. 4,256,108; 4,166,452; and
4,265,874 to form osmotic therapeutic tablets for
control release.

Formulations for oral use may also be
presented as hard gelatin capsules wherein the active
ingredient is mixed with an inert solid diluent, for

example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut (arachis) oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethylenoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial ester derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example, ethyl, or n-propyl p-hydroxybenzoate.

Oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension by mixing them with water. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oils, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth, naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial ester derived from fatty acids and hexitol anhydrides, for example, sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

An ointment containing the pharmaceutical compositions of the present invention may be prepared, among other methods known in the art, by combining the active ingredient with a medium consisting of a glycol, a lower alkanol, and water; a gelling agent; and optionally an adjuvant such as diisopropyl adipate, diethyl sebacate, ethyl caproate and ethyl laurate. Suitable glycols include propylene glycol, butylene glycol, polyethylene glycol and the like. Generally, a carboxyvinyl polymer preneutralized with an organic amine such as diisopropyl amine and triethylamine, or a cellulose, .g., hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, is used as the gelling agent.

5 The compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

10 Dosage levels of the order to 0.2 mg to 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated condition (10 mg to 7 gms per patient per day). For example, inflammation is effectively treated by the administration from about 0.5 to 50 mg of the compound per kilogram of body weight per day (25 mg to 5 gms per patient per day).

15 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain from about 25 mg to about 1 g of active ingredient.

20 It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

25 The following examples illustrate the preparation of the compounds of the formula (I) and

as such are not to be considered as limiting the invention set forth in the claims appended hereto.

5

EXAMPLE 1

Preparation of 5-Hydroxy-2,3-dihydrobenzothiophene

To a warm mixture of 5-hydroxy-benzo-
thiophene (10.0 g, 66.58 mmole) (Fieser & Kennelly,
10 J. Amer. Chem. Soc., Vol. 57, pp 1611-1614, (1935))
in 100 mL TFA was added triethylsilane (19.35 g,
166.45 mmole, 2.5 eq.) The resulting purple solution
was heated to 55°C under N₂ overnight. After 24
15 hours a sample removed for NMR analysis showed the
reaction to be about 80% complete. Much of the
original purple color had also been discharged at
this point. An additional portion of triethylsilane
(3.9 g, 0.5 eq) was added and the heating was
continued for another 24 hours. NMR analysis at the
20 48 hour time point showed virtually no change from
the 24 hour time point. Most of the TFA was
distilled off under reduced pressure (40 mmHg). The
residue was taken up in 300 mL H₂O and rendered
alkaline (pH = 10 to pH paper) with 5N NaOH and
25 washed with ether (2 X 100 mL). The aqueous phase
was acidified with 2N HCl and extracted with ether (3
x 200 mL). The combined organic extracts were washed
with sodium bicarbonate (1x100 mL), H₂O (1x100 mL)
and brine (1x100 mL). Drying over Na₂SO₄ and
30 concentration gave 4.7 g (46.5%) gray solids.
Purification by preparative chromatography on a
Waters 500A prep HPLC using 2 columns and 90/10

vol/vol hexane/EtOAc to elute afforded 3.0 g (30%)
pure material (single spot by TLC analysis) mp
87-89°C.

5

Analysis:	C	; H	; S
Calcd:	63.14	5.30	21.07
Found:	63.23	5.30	20.97

EXAMPLE 2

10

Preparation of 5-Allyloxy-2,3-dihydrobenzothiophene

15

To a solution of 5-hydroxy-2,3-dihydro-
benzothiophene (1.53 g, 10.05 mmoles) in 200 mL
acetone was added K₂CO₃ (12.5 g, 90.45 mmoles) with
good mechanical stirring. The suspension was warmed
and allyl bromide (4.86 g, 40.20 mmoles) was added in
one portion. The reaction mixture was then heated to
reflux overnight. After cooling, the solids were
removed by filtration and the filtrate concentrated.
The residue was taken up in 50/50 vol/vol hexane/
methylene chloride and refiltered to remove the
remaining salts. Concentration afforded 3.2 g crude
product (a yellow oil) which was purified by flash
chromatography (3% EtOAc in hexane to elute) to give
1.61 g pure product (83.4%) as an oil.

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Analysis:	C;	H;	S;
Calcd:	68.73	6.29	16.68
Found:	68.71	6.33	16.44

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EXAMPLE 3

Preparation of 6-Allyl-5-hydroxy-2,3-dihydrobenzo-
thiophene

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To a solution of BCl_3 in methylene chloride (5.5 mL, 1.0M, 5.5 mmole) under N_2 at -25°C was added dropwise a solution of 5-allyloxy-2,3-dihydrobenzothiophene (1.0 g, 5.2 mmole) in methylene chloride (10 mL) keeping the temperature between -25 and -15°C (10 minutes). The reaction mixture was stirred at -15°C for 15 minutes. The cooling bath was then removed and the reaction mixture allowed to stir for another 1.5 hours. The reaction mixture was then poured into ice water (70 mL). An additional portion of methylene chloride (10 mL) was added and the layers separated. The aqueous layer was extracted an additional 2 X 20 mL methylene chloride and the combined organic layers were washed with NaHCO_3 (sodium bicarbonate) (1 X 20 mL), H_2O (1 X 20 mL) and brine (1 X 20 mL). After drying over Na_2SO_4 , filtration and concentration afforded 0.56 g crude product. Purification by flash chromatography (90/10 hexane/EtOAc to elute) afforded, in order of elution: 64 mg (6.4%) 4-allyl-2,3-dihydrobenzothiophene (oil) 204 mg (20.4%) 6-allyl-2,3-dihydrobenzothiophene (oil) and 146 mg (18.4%) 5-hydroxy-2,3-dihydrobenzothiophene.

Analysis: C; H; S;
Calcd: 68.73 6.29 16.68
Found: 67.91 6.30 16.39

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EXAMPLE 4

Preparation of 6-propyl-2,3-Dihydrobenzothiophene

5 A solution of 6-allyl-2,3-dihydrobenzo-
thiophene (95 mg, 0.49 mmole) in 10 mL absolute
ethanol was hydrogenated at 40 psi over 20 mg 10%
Pd/C at room temperature overnight. TLC (90/10,
10 hexane/EtOAc) indicated the reaction to be complete.
The catalyst was filtered off through a celite pad
and the filtrate concentrated down to afford 96 mg
crude product as an oil. Purification by flash
chromatography (90/10, hexane/EtOAc) afforded 75 mg
white solids mp 58-60°C (78%).

15 Analysis: C; H; S;
Calcd: 68.00 7.26 16.20
Found: 67.91 7.13 16.45

EXAMPLE 5

20 Preparation of 6-t-Butyl-2,3-dihydrobenzothiophene

25 To a solution of 5-hydroxy-2,3-dihydro-
benzothiophene (500 mg, 3.28 mmoles) in 20 mL benzene
in a sealable tube was added t-butanol (729 mg, 9.84
mmoles, 3.0 eq) and 0.4 mL concentrated H₂SO₄. The
tube was sealed and the reaction mixture heated at
60°C for 24 hours. The reaction mixture was cooled,
diluted with water (50 mL) and extracted 2 X 25 mL
ether. The combined extracts were washed with sodium
30 bicarbonate (1 X 25 mL), H₂O (1 X 25 mL) and brine (1
X 25 mL). The organic layer was then dried over
Na₂SO₄, filtered and concentrated to give 220 mg

crude product. Purification by flash chromatography (90/10, hexane/EtOAc) afforded 125 mg pure product (18%) mp 90-93°C.

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Analysis:	C;	H;	S;
Calcd:	69.19	7.74	15.39
Found:	69.00	7.57	15.72

EXAMPLE 6

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Preparation of 5-Hydroxy-2,3-dihydro-6-(3-thiophenoxypropyl)-benzothiophene

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To a solution of 5-hydroxy-6-allyl-2,3-dihydrobenzothiophene (125 mg, 0.65 mmole) in 0.5 mL thiophenol was added 28 mg AIBN. The reaction mixture was purged with nitrogen and heated to 90°C for 3 hours. TLC analysis (90/10 hexane/EtOAc) showed the reaction to be complete. The reaction mixture was diluted with 25 mL saturated sodium bicarbonate and extracted 3 X 25 mL EtOAc. The combined organics were washed with sodium bicarbonate (2 X 25 mL), H₂O (1 X 25 mL) and brine (1 X 25 mL). Drying over Na₂SO₄, filtration and concentration afforded 568 mg crude product as an oil.

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Purification by flash chromatography (90/10, hexane/EtOAc) 126 mg (64%) pure product NMR 287 MS181.

Analysis:	C;	H;	S;
Calcd:	67.51	6.00	21.20
Found:	67.68	6.17	21.19

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While presently preferred embodiments of the invention have been described in detail for purposes of disclosure, numerous alternatives will readily

suggest themselves to those skilled in the art and
are encompassed within the principles of the
invention and the scope of the appended claims.

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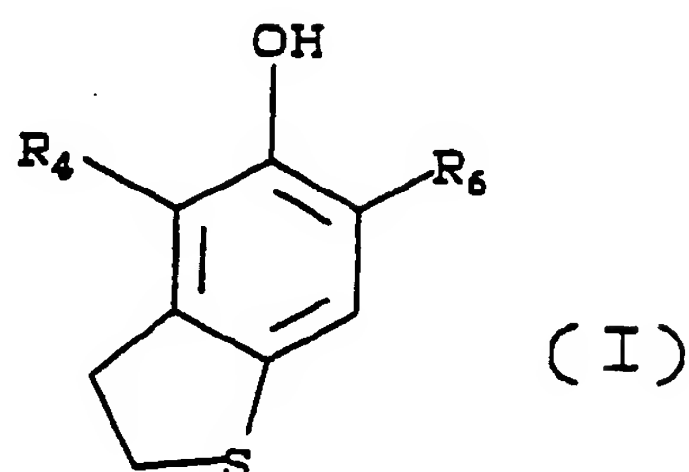
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WHAT IS CLAIMED IS:

1. A compound of formula (I)



wherein:

R₄ and R₆ are independently selected from:

- (a) hydrogen;
- (b) C₂₋₆alkenyl;
- (c) C₃₋₆alkyl; and
- (d) substituted C₃₋₆alkyl wherein the substituent is phenylthio

or pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1 wherein R₄ is hydrogen.

3. A compound according to Claim 2 wherein:
R₆ is
- (a) C₃₋₄alkenyl;
 - (b) C₃₋₄alkyl;
 - (c) phenylthio substituted C₃₋₄ alkyl.

4. A compound according the Claim 3
selected from the group consisting of:

- 5 (a) 6-(propen-3-yl)-5-hydroxy-2,3-dihydro-
benzothiophene;
- (b) 6-propyl-2,3-dihydro-5-hydroxybenzothio-
phene;
- 10 (c) 6-t-butyl-2,3-dihydro-5-hydroxybenzo-
thiophene; and
- (d) 5-hydroxy-2,3-dihydro-6-(3-thiophenoxy-
propyl)-benzothiophene,

or pharmaceutically acceptable salts thereof.

15 5. A pharmaceutical composition for
treating leukotriene mediated diseases comprising a
pharmaceutical carrier and a non-toxic effective
amount of a compound, according to Claim 1.

20 6. A pharmaceutical composition according
to Claim 5 wherein the compound is selected from the
group consisting of:

- 25 (a) 6-(propen-3-yl)-5-hydroxy-2,3-dihydro-
benzothiophene;
- (b) 6-propyl-2,3-dihydro-5-hydroxybenzothio-
phene;
- (c) 6-t-butyl-2,3-dihydro-5-hydroxybenzo-
thiophene; and
- 30 (d) 5-hydroxy-2,3-dihydro-6-(3-thiophenoxy-
propyl)-benzothiophene,

or pharmaceutically acceptable salts thereof.

7. The use of a compound as claimed in Claim 1 for the preparation of a medicament useful for treating leukotriene mediated diseases.

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